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## PALLIATIVE CARE IN ADVANCED PANCREATIC CANCER

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### Abstract

The management of patients with advanced pancreatic cancer often requires a multi-disciplinary approach with individualised therapy. Addressing the underlying causes of several of the troublesome symptoms that are relatively unique to the pathophysiology of pancreatic cancer is crucial in order to optimise the function and comfort of people diagnosed with this poor prognosis cancer. Early recognition and response is likely to improve outcomes later in the course of the disease, but more work needs to be done to compare expectant and reactive approaches to the most troublesome symptoms in advanced pancreatic cancer. Given such a poor outlook, referral to a palliative care service that has an active, team-based approach that includes dietetics, gastroenterology, interventional pain expertise and liaison psychiatry is likely to deliver the best possible outcomes. Such programs need to be in centres with sufficient caseload to ensure that meaningful outcomes can be measured prospectively and these teams are also best placed to incorporate new knowledge and approaches as the evidence base continues to evolve.

Pancreatic cancer is the fifth most common cause of death due to cancer in Australia, and the rest of the western world. In 2011, the overall five year survival was 5.2% in Australia for patients diagnosed with pancreatic cancer. If Australian trends of incidence and mortality in pancreatic cancer mirror the United States, the implication is that the incidence of pancreatic cancer will increase over the next few decades to become one of the leading causes of cancer-related mortality in Australia.<sup>1</sup> Approximately 80-85% of patients have unresectable disease at presentation,<sup>2</sup> and this group of patients can expect to have a five-year survival of 3%

in Australia.<sup>1</sup> Therefore, patients with locally advanced pancreatic cancer may benefit from early referral to a palliative care service for symptom management.

### Specific symptom management issues that relate to advanced prostate cancer

In the palliative care setting, patients with advanced cancer commonly experience symptoms such as pain, nausea and vomiting. However, advanced pancreatic cancer causes a number of other symptoms due to the anatomical location of the primary tumour and pattern

of metastatic spread, with infiltration of the liver and coeliac or splanchnic nodes. Advanced prostate cancer also predisposes patients to an increased risk of venous thrombo-embolism (VTE).

## Venous thrombo-embolism in pancreatic cancer

A diagnosis of cancer carries a hundred-fold increased risk of venous VTE compared with the healthy population. Pancreatic cancer has an increased incidence of VTE compared with all other cancer populations. The rate of presentation with VTE has recently been reported to be 11.6% at three months and 21.3% at 12 months after diagnosis in advanced pancreatic cancer.<sup>3</sup> The increase in VTE risk is thought to be due to cancer cell over-expression of tissue factor and mucin, and this leads to a hypercoagulable state. Over-expression of tissue factor and mucin occur more frequently with primary tumours originating within the body and the tail of the pancreas than in the head. This may explain the increased incidence in VTE in body and tail tumours, and a worse prognosis in these patients.<sup>4</sup> Where patients with advanced pancreatic cancer present with abdominal pain, inferior vena cava or splanchnic vein thrombosis should be considered in the differential cause.

The CLOT study in 2003 demonstrated that low molecular weight heparin (LMWH) dalteparin produced better overall survival and fewer bleeding events than warfarin. LMWH has been the gold standard treatment of VTE in cancer.<sup>5</sup> Since then, rivaroxaban has been introduced to reduce the risk of stroke in atrial fibrillation. The advantages of rivaroxaban over LMWH and warfarin are that it is taken by tablet once a day and does not require any therapeutic monitoring. However, there have been no studies published to date that prove superiority of the use of rivaroxaban in the treatment of VTE in cancer patients. The role of primary prevention of VTE in advanced pancreatic cancer is being elucidated. The PROSPECT-CONKO 004 study showed that the greatest reduction in VTE events was in the first three months after patients commenced chemotherapy in combination with treatment with enoxaparin compared with chemotherapy alone.<sup>3</sup> As expected, there was also an increased risk of major bleeding in the enoxaparin group (8.3% in the enoxaparin group vs 6.9% in the observation group). The study was not powered to determine the safety of enoxaparin in the trial conditions. Further studies are awaited to determine the role of thromboprophylaxis in the management of patients with advanced pancreatic cancer who have supportive care alone.

## Pancreatic exocrine insufficiency

Pancreatic exocrine insufficiency (PEI) occurs as cells, which synthesise pancreatic enzymes, are either progressively destroyed by pancreatic cancer cells, or the main pancreatic duct is blocked by a tumour within the anatomical head of the pancreas, where the majority of tumours occur.<sup>6,7</sup> This causes compression of the

proximal pancreatic duct, and endoscopic stenting may be required. Consultation with a gastroenterologist will determine the role for investigation with endoscopic retrograde cholangiopancreatography and insertion of a biliary stent. Untreated blockage at the head of the pancreas causes progressive loss of exocrine function of the pancreas, and patients will experience symptoms of PEI resulting in deterioration in the patient's quality of life and overall survival.<sup>8,9</sup> The incidence of PEI is estimated to be around 85% when patients present with pancreatic cancer.<sup>10</sup>

PEI occurs in other disorders of the pancreas such as cystic fibrosis, chronic pancreatitis and following pancreatic resection. PEI has been extensively studied in these non-malignant conditions, but not in advanced pancreatic cancer. Symptoms arise due to malabsorption of fat, and these include weight loss, diarrhoea, steatorrhoea, flatulence, abdominal pain and bloating. PEI may also cause fat-soluble vitamin deficiencies.

The mechanism for treating PEI in pancreatic cancer with pancreatic enzyme replacement therapy (PERT) was elucidated in a small study from the Mayo Clinic in 1983.<sup>11</sup> Guidelines, based on studies with small numbers of patients, recommend the empiric treatment of symptomatic patients with PERT.<sup>7,12,13</sup> Patients who have undergone pancreatic resection are prescribed PERT based on their risk of PEI.<sup>2</sup> Yet patients who have advanced pancreatic cancer are not routinely evaluated for symptoms of PEI, referred to a dietitian or offered PERT.<sup>14</sup> There is evidence that patients often try dietary fat restriction or other therapies to manage their symptoms, and have a variable degree of success in managing of PEI.<sup>15</sup>

The most commonly prescribed PERT is an encapsulated form of pancreatic enzymes derived from porcine pancreas. Its safety profile has been established in cystic fibrosis and chronic pancreatitis.<sup>16</sup> Successful treatment with PERT requires education by a dietitian to explain the timing of medication with relation to meals. Individualised therapy may be required, including, for example, a change in dose or the addition of a proton pump inhibitor, which aids the activation of PERT if the gut pH is too low. Patients who are on treatment require monitoring and treatment algorithms have been published.<sup>17</sup> Data on the success of treatment with PERT in advanced pancreatic cancer have not been published to date. For patients who have treatment failure, further investigation can exclude the presence of bacterial overgrowth.<sup>18</sup>

## Cachexia in advanced pancreatic cancer

Cachexia arises as a consequence of release of systemic cytokines and PEI in advanced pancreatic cancer, and is known to have an adverse effect upon overall survival of patients who present with resectable pancreatic cancer.<sup>9</sup> This study compared patients who had cachexia at presentation with pancreatic cancer and those who did not, and found that patients who

cachexia at presentation had poorer overall survival at 12 months post-operatively compared with patients who did not. It has been demonstrated that PERT can prevent weight loss in advanced pancreatic cancer,<sup>19</sup> but no definitive studies have established that there is a survival advantage with PERT. The hypothesis that treatment of cachexia and PEI in advanced pancreatic cancer may result in improvement of patient quality of life and prognosis is unproven in clinical trials.

## Pain and pancreatic cancer

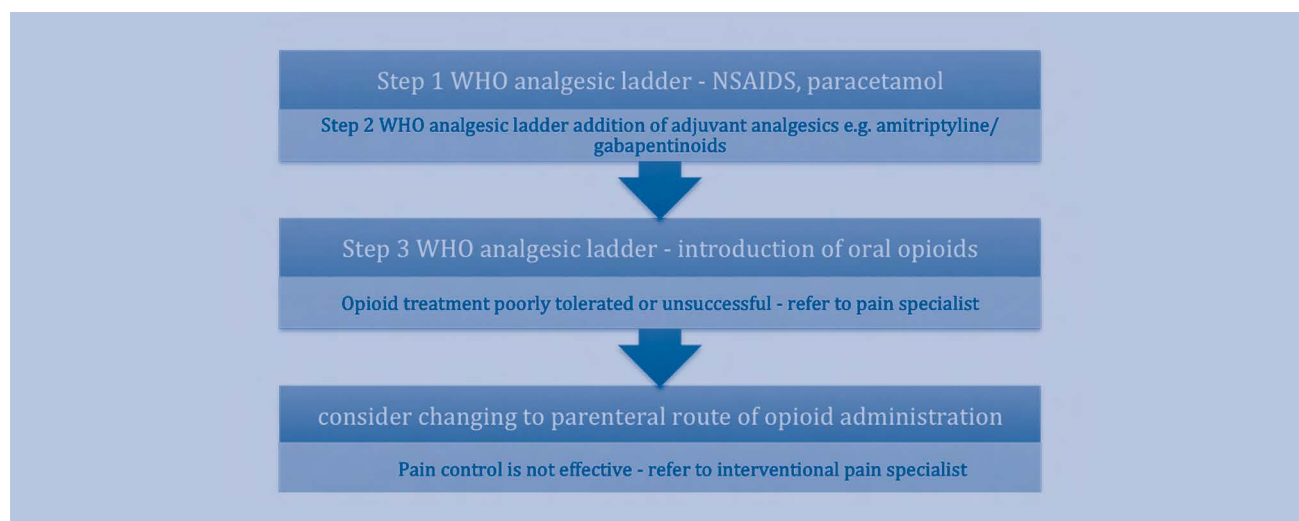
Pain management is a challenging issue and affects 50-70% of patients who are diagnosed with pancreatic cancer. The principles of management have not changed significantly since Russell Portenoy published an article on this area in 1996.<sup>20</sup> Pain caused by pancreatic cancer can be multi-factorial in aetiology and accurate diagnosis is essential in successful management. Perception of pain may be increased if depression coexists in advanced cancer. The incidence of depression in patients who have been diagnosed with pancreatic cancer has been reported to be as high as 41-71%.<sup>21</sup> Pain in pancreatic cancer can be neuropathic in nature, especially where there is infiltration of the coeliac plexus and may require treatment with a combination of opioid and adjuvant analgesics (see figure 1).

When there is treatment failure with oral opioids, alternative routes of administration can be considered, such as transdermal, subcutaneous or intravenously. Patients can also be referred for consideration of an interventional procedure such as a coeliac plexus block. There is considerable regional variation in access to interventional pain specialists within Australia, and patients in rural locations may travel to a major tertiary referral centre for assessment. A recent Cochrane Collaboration review of coeliac plexus blocks for pain in advanced pancreatic cancer did not demonstrate a durable benefit in analgesia with this technique. However, there was an objective reduction in oral opioids taken by patients who underwent the procedure compared with those who were managed conservatively and they experienced fewer side-effects from opioid administration.<sup>24</sup>

## Liver metastases

Advanced pancreatic cancer commonly metastasises to the liver, causing progressive liver failure with jaundice, ascites, lymphoedema and hepatic encephalopathy. Biliary stenting may be complicated by ascending cholangitis and this can require treatment with intravenous antibiotics or replacement of the biliary stent. It is known from private billing data from the United States that chemotherapy is more commonly delayed for patients

**Figure 1:** Management of pain due to coeliac plexus infiltration.



Recently the anticonvulsants gabapentin and pregabalin have been introduced in the management of neuropathic pain. Treatment failure with these agents may occur for different reasons. Pregabalin has been studied in pain due to chronic pancreatitis and its absorption profile is unaltered in this condition.<sup>22,23</sup> However, it is not known whether alteration in gastrointestinal motility caused by opioids, which are commonly co-prescribed in cancer pain, has an effect upon the absorption of adjuvant analgesics, or whether PEI and its treatment influences the absorption of orally administered analgesics.

who have plastic endoprosthetic stents than metallic stents, as plastic stents are more frequently blocked and colonised by bacteria than metallic stents.<sup>25,26</sup> It is worthwhile to consider replacement of a stent if colonisation is suspected.<sup>21,26</sup> Pruritis occurs with jaundice, and treatment options with a variety of agents from different classes have been reported in clinical trials. These include rifampicin, cholestyramine and ondansetron.<sup>27</sup> However, due to the small numbers of participants in studies considered in a Cochrane review on pruritis in palliative care, it was only possible for the

authors to recommend that good quality further studies are needed in this area.

Ascites can be a difficult symptom to manage. Successful treatment with diuretics such as spironolactone is enhanced when the intra-abdominal volume of ascites is relatively small by clinical evaluation, which is more likely at an early stage in the illness. More established ascites is likely to be refractory to diuretics, even with a combination of class agents, and ascitic drainage may be required.<sup>28</sup> In some centres this is done under radiological guidance. Where repeated abdominal paracentesis is required, permanent drains such as Tenckhoff catheter (peritoneal dialysis catheter) or tunneled PleurX drains can be used. The insertion of a drain of this type means that patients can be managed successfully at home without attending a hospital appointment or being admitted as an inpatient to have a procedure.<sup>29</sup>

## Conclusion

Patients with pancreatic cancer often present with advanced disease, for which there are no curative options. There is evidence that conditions which co-exist in pancreatic cancer such as pain, depression, cachexia and pancreatic exocrine insufficiency are under-treated. A multi-disciplinary approach to management can have a positive impact on quality of life in a condition that is predicted to increase in prevalence over the next few decades and currently has limited options for disease modification.

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